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Attorney Docket No. OPHD-03282

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: John A. Kink
Serial No.: 09/095,536 Group No.: 1646
Filed: 06/10/98 Examiner: Hamud, F.
Entitled: **Prevention and Treatment of Sepsis**

INFORMATION DISCLOSURE STATEMENT TRANSMITTAL

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Assistant Commissioner for Patents
Washington, D.C. 20231

CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Dated: November 30, 1999 By: Christopher J. Collins

Sir or Madam:

Enclosed please find an Information Disclosure Statement and Form PTO-1449, including copies of the references contained thereon, for filing in the U.S. Patent and Trademark Office.

A check for $240.00 is also enclosed pursuant to 37 C.F.R. § 1.17(p) for filing this Information Disclosure Statement after three months as set forth in 37 C.F.R. § 1.97(c).

The Commissioner is hereby authorized to charge any additional fee or credit overpayment to our Deposit Account No. **08-1290**. **An originally executed duplicate of this transmittal is enclosed for this purpose.**

Dated: November 30, 1999

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Christopher J. Collins

Sir or Madam:

The citations listed below, copies attached, may be material to the examination of the above-identified application, and are therefore submitted in compliance with the duty of disclosure defined in 37 C.F.R. §§ 1.56 and 1.97. The Examiner is requested to make these citations of official record in this application.

The following printed publications are discussed in the body of the specification:

- Machiedo *et al.*, "Patterns of Mortality in a Surgical Intensive Care Unit," *Surg. Gyn. & Obstet.* 152:757-759 (1981);
- Morris *et al.*, "Endotoxemia in neonatal calves given antiserum to a mutant *Escherichia coli* (J-5)," *Am. J. Vet. Res.* 47:2554-2565 (1986);
- Hoffman *et al.*, "Prognostic Variables for Survival of Neonatal Foals Under Intensive Care," *J.Vet. Int. Med.* 6:89-95 (1992);
- Wolff, "Monoclonal Antibodies and the Treatment of Gram-Negative Bacteremia and Shock," *New Eng. J. Med.* 324:486-488 (1991);

- K.A. Schulman *et al.*, "Cost-effectiveness of HA-1A Monoclonal Antibody for Gram-Negative Sepsis," *JAMA* 266:3466-3471 (1991);
- K. Ohlsson *et al.*, "Interleukin-1 receptor antagonist reduces mortality from endotoxin shock," *Nature* 348:550-552 (1990);
- R.C. Bone, "The Pathogenesis of Sepsis," *Ann. Intern. Med.* 115:457-469 (1991);
- K.J. Tracey *et al.*, "Shock and Tissue Injury Induced by Recombinant Human Cachectin," *Science* 234:470-474 (1986);
- A. Tewari *et al.*, "Preliminary report: effects of interleukin-1 on platelet counts," *Lancet* 336:712-714 (1990);
- S.M. Opal *et al.*, "Efficacy of a Monoclonal Antibody Directed against Tumor Necrosis Factor in Protecting Neutropenic Rats from Lethal Infection with *Pseudomonas aeruginosa*," *J. Infect. Dis.* 161:1148-1152 (1990);
- Polson *et al.*, "Antibodies to Proteins from Yolk of Immunized Hens," *Immunol. Comm.*, 9:495 (1980);
- C. Galanos *et al.*, "Galactosamine-induced sensitization to the lethal effects of endotoxin," *Proc. Natl. Acad. Sci. USA* 76:5939-5943 (1979);
- J. Rothe *et al.*"Mice lacking the tumor necrosis factor receptor 1 are resistant to TNF-mediated toxicity but highly susceptible to infection by Listeria monocytogenes," *Nature* 364:798-802 (1993); and
- S.Q. DeJoy *et al.*, "Effect of CL 184,005, a Platelet-Activating Factor Antagonist in a Murine Model of *Staphylococcus auteus*-Induced Gram-Positive Sepsis," *J. Infect. Dis.* 169:150-156 (1994).

Applicant has become aware of the following printed publication which may be material to the examination of this application:

- Opal et al., "Potential Hazards of Combination Immunotherapy in the Treatment of Experimental Septic Shock," *J. of Infectious Diseases* 173:1415-1421 (1996) describes a combination anticytokine approach for the treatment of sepsis in rats utilizing two linked recombinant human TNF type 1 receptors and a human interleukin-1 receptor antagonist. This combination proved to be

uniformly fatal. In contrast to the present invention as claimed, Opal et al. do not disclose a composition comprising purified antibodies to TNF and IL-6;

- Russell et al., "Combined Inhibition of Interleukin-1 and Tumor Necrosis Factor in Rodent Endotoxemia: Improved Survival and Organ Function," *J. of Infectious Diseases* 171:1528-1538 (1995) describes a combination anticytokine approach for the treatment of sepsis in rats utilizing two linked TNF receptors and a human interleukin-1 receptor antagonist. In contrast to the present invention as claimed, Russell et al. do not disclose a composition comprising purified antibodies to TNF and IL-6;
- PCT Patent Application No. WO9633204 describes a method of treating an individual having a TNF-mediated disease comprising administering to the individual multiple doses of an anti-TNF antibody. Anti-TNF antibodies can be administered alone or in conjunction with other therapeutic agents. In contrast to the present invention as claimed, the application does not disclose a composition comprising purified antibodies to TNF and IL-6;
- Plevy *et al.*, "A Role for TNF-α and Mucosal T Helper-1 Cytokines in the Pathogenesis of Crohn's Disease," *J. of Immunology* 159:6277-6282 (1997) investigate the role of chimeric antibody in cytokine production using TNF-alpha and IFN-gamma-producing cells. Patients suffering from Crohn's disease were administered one injection of monoclonal antibody. In contrast to the present invention as claimed, Plevy et al. does not disclose a composition comprising purified antibodies to TNF and IL-6;
- Van Dullemen *et al.*, "Treatment of Crohn's Disease With Anti-Tumor Necrosis Factor Chimeric Monoclonal Antibody (cA2)," *Gastroenterology* 109:129-138 (1995), describe the use of an a single injection of anti-TNF monoclonal antibody in the treatment of Crohn's disease. In contrast to the present invention as claimed, Van Dullemen et al. do not disclose a composition comprising purified antibodies to TNF and IL-6;
- Targan *et al.*, "A Short-Term Study of Chimeric Monoclonal Antibody cA2 to Tumor Necrosis Factor α for Crohn's Disease," NEJM, 337:1029-1035 (1997) describe the use of a chimeric monoclonal antibodies to TNF in the treatment

of Crohn's disease. Patients were given a single infusion of antibody. In contrast to the present invention as claimed, Targan et al. do not disclose a composition comprising purified antibodies to TNF and IL-6;

- Elliott *et al.*, "Randomised double-blind comparison of chimeric monoclonal antibody to tumor necrosis factor α (cA2) versus placebo in rheumatoid arthritis," *Lancet* 344:1105-1110 (1994), describe the use of anti-TNFα antibody in treatment of rheumatoid arthritis. Chimeric monoclonal antibodies to TNFα were administered to patients. In contrast to the present invention as claimed, Elliott et al. do not disclose a composition comprising purified antibodies to TNF and IL-6;
- Elliott *et al.*, "Repeated therapy with monoclonal antibody to tumor necrosis factor α (cA2) in patients with rheumatoid arthritis," *Lancet* 344:1125-1127 (1994), describe the use of repeated treatments of rheumatoid arthritis with anti-TNFα monoclonal antibody. This article suggests that repeated treatments with the antibody may be necessary for effective management of the disease. In contrast to the present invention as claimed, Elliott et al. do not disclose a composition comprising purified antibodies to TNF and IL-6;
- Kojouharoff et al., " Neutralization of tumor necrosis factor (TNF) but not of IL-1 reduces inflammation in chronic dextran sulphate sodium-induced colitis in mice," *Clin Exp Immunol* 107:353-358 (1997), describe the use of rat anti-mouse TNF monoclonal antibody *or* mouse anti-mouse IL-1beta monoclonal antibody to treat dextran sulphate sodium induced inflammatory bowel disease in mice. In contrast to the present invention as claimed, Kojouharoff et al. do not disclose a composition comprising purified antibodies to TNF and IL-6;
- Olson et al., "Antiserum to Tumor Necrosis Factor and Failure to Prevent Murine Colitis," *J Ped Gastroenterology Nutrition* 21:410-418 (1995), describe the use of anti-TNF polyclonal antibodies to treat dextran sulphate sodium induced Crohn's colitis in mice. In contrast to the present invention as claimed, Olson et al. do not disclose a composition comprising purified antibodies to TNF and IL-6;

- US Patent No. 5,654,407 to Boyle *et al.* describes human monoclonal antibodies to TNFα. The patent also discloses the introduction of the antibody into patients where TNF production contributes to the disease process or state. In contrast to the present invention as claimed, Boyle et al. do not disclose a composition comprising purified antibodies to TNF and IL-6;
- US Patent No. 5,436,154 to Barbanti *et al.* describes the development of a monoclonal antibodies to TNFα and TNFβ, or a binding fragment thereof, as well as a cell line capable of secreting the antibody. Barbanti discloses that antibodies against TNFα could be therapeutically useful in disease states in which TNFα exerts a pathogenic effect, including chronic inflammatory diseases. Polyclonal antibodies to TNFα are also discussed. In contrast to the present invention as claimed, Barbanti et al. do not disclose a composition comprising purified antibodies to TNF and IL-6;
- US Patent No. 5,385,901 to Kaplan *et al.* describes a method treating abnormal concentrations of TNFα. Formulas of chemical compounds which inhibit the production of TNFα are described. In contrast to the present invention as claimed, Kaplan et al. do not disclose a composition comprising purified antibodies to TNF and IL-6;
- US Patent No. 4,870,163 to Rubin *et al.* describes the preparation of pure human TNF and hybridomas producing monoclonal antibodies to TNF. The patent relates to a sequential chromatographic process for the purification of a human TNF produced by the LuKII cell line. In contrast to the present invention as claimed, Rubin et al. do not disclose a composition comprising purified antibodies to TNF and IL-6; and
- US Patent No. 5,656,272 to Le *et al.* discloses methods of treating TNFα-mediated Crohn's disease using chimeric anti-TNF antibodies. In contrast to the present invention as claimed, Le et al. do not disclose a composition comprising purified antibodies to TNF and IL-6.
- Zacharchuk *et al.*, "Macrophage-mediated cytotoxicity: Role of a soluble macrophage cytotoxic factor similar to lymphotoxin and tumor necrosis factor," *PNAS USA* 80:6341-6345 (1983) discloses guinea pig peritoneal macrophages

produce a cytotoxic factor found to have a molecular weight of 45,000. The factor was neutralized by anti-lymphotoxin antibodies.

- Zacharchuk, Charles Michael, "A Macrophage Cytotoxic Factor: Immunochemical and Functional Characterization," Dissertation Abstract. The abstract discloses the same results as the reference above (Zacharchuk *et al.*, "Macrophage-mediated cytotoxicity: Role of a soluble macrophage cytotoxic factor similar to lymphotoxin and tumor necrosis factor," *PNAS USA* 80:6341-6345 (1983)).
- Pennica *et al.*, "Human tumor necrosis factor: precursor structure, expression and homology to lymphotoxin," *Nature* 312:724-729 (1984) reports human tumor necrosis factor has about 30% homology in its amino acid sequence with lymphotoxin, a lymphokine that has similar biological properties.
- Ruff, Michael Roland, "Mechanism of Action of a Serum Oncolytic Protein, Rabbit Tumor Necrosis Factor," Dissertation Abstract. Discuss Rabbit Tumor Necrosis Factor.

This Information Disclosure Statement under 37 C.F.R. §§ 1.56 and 1.97 is not to be construed as a representation that a search has been made, that additional information material to the examination of this application does not exist, or that any one or more of these citations constitutes prior art.

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